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5.21.050

Section:	Prescription Drugs	**Effective Date:**	October 1, 2025
Subsection:	Antineoplastic Agents	**Original Policy Date:**	September 26, 2014
Subject:	Keytruda	**Page:**	1 of 18

Last Review Date: September 19, 2025

Keytruda

Description

Keytruda (pembrolizumab)

Background
Keytruda (pembrolizumab) is a monoclonal antibody for the treatment of patients with many different types of cancer. Keytruda blocks a cellular pathway known as PD-1, human programmed death receptor-1, which restricts the body's immune system from attacking cancer cells (1-2).

Regulatory Status
FDA-approved indications: Keytruda is a human programmed death receptor-1 (PD-1)-blocking antibody indicated: (1)

1. Melanoma
    a. For the treatment of patients with unresectable or metastatic melanoma
    b. For the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection
2. Non-Small Cell Lung Cancer (NSCLC)
    a. In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations
    b. In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC
    c. As a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA approved test with no EGFR or ALK genomic tumor aberrations, and is:

i. Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
ii. Metastatic.

d. As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda.
e. for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
f. As a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage IB (T2a ≥4 cm), II, or IIIA NSCLC.

3. Malignant Pleural Mesothelioma (MPM)
   a. In combination with pemetrexed and platinum chemotherapy, as first-line treatment of adult patients with unresectable advanced or metastatic MPM
4. Head and Neck Squamous Cell Cancer (HNSCC)
   a. In combination with platinum and fluorouracil (FU), for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
   b. As a single agent, for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.
   c. As a single agent, for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
5. Classical Hodgkin Lymphoma (cHL)
   a. For the treatment of adult patients with relapsed or refractory cHL
   b. For the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy
6. Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
   a. For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy
   b. Limitations of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
7. Urothelial Carcinoma
   a. In combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma
   b. As a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma:

i. who are not eligible for any platinum-containing chemotherapy, or
ii. who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

c. As a single agent for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy

8. Microsatellite Instability-High or Mismatch Repair Deficient Cancer
   a. For the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options
9. Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)
   a. For the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test
10. Gastric Cancer
   a. In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test
   b. In combination with fluoropyrimide- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA approved test
11. Esophageal Cancer
   a. For the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
      i. In combination with platinum- and fluoropyrimidine-based chemotherapy for patients whose tumors express PD-L1 (CPS ≥1), or
      ii. As a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test
12. Cervical Cancer

a. In combination with chemoradiotherapy, for the treatment of patients with locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA)
b. In combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test
c. As a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test

13. Hepatocellular Carcinoma (HCC)
    a. For the treatment of patients with HCC secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen
14. Biliary Tract Cancer (BTC)
    a. In combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer
15. Merkel Cell Carcinoma (MCC)
    a. For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma
16. Renal Cell Carcinoma (RCC)
    a. In combination with axitinib, for the first-line treatment of patients with advanced RCC
    b. In combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC
    c. For the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions
17. Endometrial carcinoma
    a. In combination with carboplatin and paclitaxel, followed by Keytruda as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma
    b. In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not MSI-H as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation
    c. As a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by and FDA-approved test,

who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation

18. Tumor Mutational Burden-High (TMB-H) Cancer
    a. For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options
    b. Limitations of Use: The safety and effectiveness of Keytruda in pediatric patients with TMB-H central nervous system cancers have not been established.
19. Cutaneous Squamous Cell Carcinoma (cSCC)
    a. For the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation
20. Triple-Negative Breast Cancer (TNBC)
    a. For treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery
    b. In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test
21. Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400 mg every 6 weeks
    a. For use at an additional recommended dosage of 400 mg every 6 weeks for Classical Hodgkin Lymphoma and Primary Mediastinal Large B-Cell Lymphoma in adults

Clinically significant immune-mediated adverse reactions may occur with Keytruda therapy including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, hypothyroidism, skin adverse reactions, infusion-related reactions, and other immune-mediated adverse reactions. Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued and corticosteroids administered. Patients should be monitored for signs and symptoms of pneumonitis, colitis, hypophysitis, thyroid disorders, and changes in liver and renal function. Keytruda may cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential should be advised of the potential hazard to a fetus (1).

Keytruda in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to Keytruda alone (1).

The safety and effectiveness of Keytruda have been established in pediatric patients (1).

Related Policies
Bavencio, Jemperli, Loqtorzi, Opdivo, Opdualag, Tecentriq, Zynyz

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Keytruda may be considered **medically necessary** if the conditions indicated below are met.

Keytruda may be considered **investigational** in patients with all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Unresectable or metastatic melanoma

2. Stage IIB, IIC, or III melanoma following complete resection

    a. Used as adjuvant treatment

3. Metastatic non-small cell lung cancer (NSCLC)
    a. Used as a single agent
    b. PD-L1 tumor expression with Tumor Proportion Score (TPS) ≥ 1% determined by an FDA-approved test with **ONE** of the following:
        i. Negative for EGFR or ALK tumor expression and **ONE** of the following:
            i. Disease progression on or after platinum-containing chemotherapy
            ii. First-line treatment
        ii. Positive EGFR or ALK tumor expression
            1) Disease progression after targeted FDA-approved therapy

4. Metastatic nonsquamous non-small cell lung cancer (NSCLC)

a. Used in combination with pemetrexed and platinum chemotherapy as first-line treatment
b. Negative for EGFR or ALK tumor expression

5. Stage III non-small cell lung cancer (NSCLC)
    a. Patient is not a candidate for surgical resection or definitive chemoradiation
    b. PD-L1 tumor expression with Tumor Proportion Score (TPS) ≥ 1% as determined by an FDA-approved test
    c. Negative for EGFR or ALK tumor aberrations
    d. Used as a single agent for first-line treatment

6. Stage IB (T2a ≥4cm), II, or IIIA non-small cell lung cancer (NSCLC)
    a. Used as a single agent
    b. Used as adjuvant treatment following resection and platinum-based chemotherapy

7. Resectable (tumors ≥4cm or node positive) non-small cell lung cancer (NSCLC)
    a. Used as neoadjuvant treatment
    b. Used in combination with platinum-containing chemotherapy
    c. Will be used as a single agent after resection

8. Metastatic squamous non-small cell lung cancer (NSCLC)
    a. Used in combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment

9. Unresectable advanced or metastatic malignant pleural mesothelioma (MPM)
    a. Used in combination with pemetrexed and platinum chemotherapy as first-line treatment

10. Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) and **ONE** of the following:
    a. Used in combination with platinum and fluorouracil (FU) as first-line treatment
    b. PD-L1 tumor expression with combined positive score (CPS) ≥ 1 as determined by an FDA-approved test
        i. Used as a single agent for first-line treatment
    c. Disease progression on or after platinum-containing chemotherapy
        i. Used as a single agent

11. Classical Hodgkin lymphoma (cHL) with **ONE** of the following:

a. Refractory cHL
b. Relapsed cHL
    i. Age < 18 **only**: patient has relapsed after 2 or more prior lines of therapy

12. Refractory primary mediastinal large B-cell lymphoma (PMBCL)
    a. Patient has relapsed after 2 or more lines of therapy

13. Locally advanced or metastatic urothelial carcinoma with **ONE** of the following:
    a. Used in combination with Padcev (enfortumab vedotin)
    b. Patient is **NOT** eligible for any platinum-containing chemotherapy
        i. Used as a single agent
    c. Disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
        i. Used as a single agent

14. Non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS)
    a. Bacillus Calmette-Guerin (BCG)-unresponsive
    b. Patient is considered high-risk
    c. Patient is ineligible for or has elected not to undergo cystectomy

15. Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors
    a. MSI-H or dMMR tumor status, as determined by an FDA-approved test
    b. Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options

16. Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC)
    a. MSI-H or dMMR tumor status, as determined by an FDA-approved test

17. Locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma
    a. Used in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy
    b. Used as first-line treatment
    c. PD-L1 tumor expression with combined positive score (CPS) ≥ 1 as determined by an FDA-approved test

18. Locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma
    a. Used in combination with fluoropyrimidine- and platinum-containing chemotherapy
    b. Used as first-line treatment
    c. PD-L1 tumor expression with combined positive score (CPS) ≥ 1 as determined by an FDA-approved test

19. Locally advanced or metastatic esophageal or gastroesophageal junction carcinoma
    a. Carcinoma is not amenable to surgical resection or definitive chemoradiation
    b. Keytruda is being used as **ONE** of the following:
        i. In combination with platinum- and fluoropyrimidine-based chemotherapy **AND** PD-L1 tumor expression with combined positive score (CPS) ≥ 1
        ii. As a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test

20. Cervical cancer with **ONE** of the following:
    a. FIGO 2014 Stage III-IVA cervical cancer
        i. Used in combination with chemoradiotherapy
    b. Persistent, recurrent, or metastatic cervical cancer
        i. Used in combination with chemotherapy
        ii. PD-L1 tumor expression with combined positive score (CPS) ≥ 1 as determined by an FDA-approved test
    c. Recurrent or metastatic cervical cancer
        i. Used as a single agent
        ii. Disease progression on or after chemotherapy
        iii. PD-L1 tumor expression with combined positive score (CPS) ≥ 1 as determined by an FDA-approved test

21. Hepatocellular carcinoma (HCC)
    a. HCC secondary to hepatitis B
    b. Patient has received prior systemic therapy other than a PD-1/PD-L1-containing regimen

22. Locally advanced unresectable or metastatic biliary tract cancer (BTC)

a. Used in combination with gemcitabine and cisplatin

23. Recurrent locally advanced or metastatic Merkel cell carcinoma (MCC)

24. Advanced renal cell carcinoma (RCC) **AND ONE** of the following:
    a. First-line treatment
        i. Used in combination with Inlyta (axitinib) **OR** Lenvima (lenvatinib)
        ii. Prescriber agrees to monitor for hepatotoxicity
    b. Adjuvant treatment in patients with **ONE** of the following:
        i. Intermediate-high or high risk of recurrence following nephrectomy
        ii. Following nephrectomy and resection of metastatic lesions

25. Endometrial carcinoma
    a. Patient has **ONE** of the following:
        i. Primary advanced or recurrent endometrial carcinoma
            1. Used in combination with carboplatin and paclitaxel, followed by Keytruda as a single agent
        ii. Advanced endometrial carcinoma
            1. Disease progression following prior systemic therapy
            2. **NOT** a candidate for curative surgery or radiation
            3. **AND ONE** of the following:
                a. MSI-H or dMMR tumor status, as determined by an FDA-approved test
                    i. Used as a single agent
                b. Mismatch repair proficient (pMMR) or **NOT** MSI-H as determined by an FDA-approved test
                    i. Used in combination with Lenvima (lenvatinib)

26. Unresectable or metastatic tumor mutational burden-high (TMB-H) solid tumors
    a. ≥10 mutations/megabase (mut/Mb) as determined by an FDA-approved test
    b. Disease has progressed following prior treatment
    c. Patient has no satisfactory alternative treatment options

d. **NOT** for use in pediatric patients with TMB-H central nervous system cancers

27. Recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC
    a. **NOT** curable by surgery or radiation

28. Triple-Negative Breast Cancer (TNBC) and **ONE** of the following:
    a. High-risk early-stage TNBC
        i. Used in combination with chemotherapy as neoadjuvant treatment **OR**
        ii. Used as a single agent after surgery as adjuvant treatment
    b. Locally recurrent unresectable or metastatic TNBC
        i. PD-L1 tumor expression with combined positive score (CPS) ≥ 10 as determined by an FDA-approved test
        ii. Used in combination with chemotherapy

AND ALL of the following for **ALL** indications:
a. Prescriber agrees to discontinue treatment for any immune mediated adverse reaction (encephalitis, nephritis, rash, decreased renal function and endocrinopathies) or disease progression
b. Female patients of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Keytruda and for 4 months after the last dose

Prior – Approval *Renewal* Requirements

Diagnoses

Patient must have **ONE** of the following:
1. Unresectable or metastatic melanoma
2. Stage IIB, IIC, or III melanoma following complete resection
3. Metastatic non-small cell lung cancer (NSCLC)
4. Metastatic nonsquamous non-small cell lung cancer (NSCLC)
5. Stage III non-small cell lung cancer (NSCLC)
6. Stage IB (T2a ≥4cm), II, or IIIA non-small cell lung cancer (NSCLC)
7. Non-small cell lung cancer (NSCLC) following resection
8. Metastatic squamous non-small cell lung cancer (NSCLC)
9. Unresectable advanced or metastatic malignant pleural mesothelioma (MPM)

10. Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)
11. Relapsed or refractory classical Hodgkin lymphoma (cHL)
12. Refractory primary mediastinal large B-cell lymphoma (PMBCL)
13. Locally advanced or metastatic urothelial carcinoma
    a. Used as a single agent **OR** used in combination with Padcev (enfortumab vedotin)
14. Non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS)
15. Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors
16. Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer
17. Locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma
    a. Used in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy
18. Locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma
    a. Used in combination with fluoropyrimidine- and platinum-containing chemotherapy
19. Locally advanced or metastatic esophageal or gastroesophageal junction carcinoma
20. Persistent, recurrent, or metastatic cervical cancer **OR** FIGO 2014 Stage III-IVA cervical cancer
21. Hepatocellular carcinoma (HCC)
22. Locally advanced unresectable or metastatic biliary tract cancer (BTC)
    a. Used in combination with gemcitabine and cisplatin
23. Recurrent locally advanced or metastatic Merkel cell carcinoma (MCC)
24. Advanced renal cell carcinoma (RCC) **AND ONE** of the following:
    a. First-line treatment
        i. Used in combination with Inlyta (axitinib) **OR** Lenvima (lenvatinib)
        ii. Prescriber agrees to monitor for hepatotoxicity
    b. Adjuvant treatment
25. Endometrial carcinoma **AND ONE** of the following
    a. Used as a single agent for advanced, primary advanced, or recurrent endometrial carcinoma
    b. Used in combination with Lenvima (lenvatinib) for advanced endometrial carcinoma
26. Unresectable or metastatic tumor mutational burden-high (TMB-H) solid tumors
    a. **NOT** for use in pediatric patients with TMB-H central nervous system cancers

27. Recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC
28. Triple-negative breast cancer (TNBC) and **ONE** of the following:
    a. High-risk early-stage TNBC used as single agent as adjuvant treatment
    b. Locally recurrent unresectable or metastatic TNBC used in combination with chemotherapy

AND the following:

a. Prescriber agrees to discontinue treatment for any immune mediated adverse reaction (encephalitis, nephritis, rash, decreased renal function and endocrinopathies) or disease progression
b. Female patients of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Keytruda and for 4 months after the last dose

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Keytruda (pembrolizumab) is a monoclonal antibody indicated for the treatment of patients with many different types of cancer. Clinically significant immune-mediated adverse reactions may occur with Keytruda therapy including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, hypothyroidism, skin adverse reaction, infusion-related reactions, and other immune-mediated adverse reactions. Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued, and corticosteroids administered. Keytruda may cause fetal harm when administered to a pregnant woman. The safety and effectiveness of Keytruda have been established in pediatric patients (1-2).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Keytruda while maintaining optimal therapeutic outcomes.

References

1. Keytruda [package insert]. Rahway, NJ: Merck Sharp & Dohme Corp.; July 2025.
2. NCCN Drugs & Biologics Compendium® Pembrolizumab 2025. National Comprehensive Cancer Network, Inc. Accessed on July 28, 2025.

Policy History

Date	Action
September 2014	New policy
December 2014	Annual editorial review and reference update
June 2015	Annual editorial review
October 2015	Addition of Metastatic non-small cell lung cancer (NSCLC) if the patient has PD-L1 tumor expression determined by a FDA-approved test and has disease progression on or after platinum-containing chemotherapy; or the patient has EGFR or ALK tumor expression and has disease progression after FDA-approved therapy
December 2015	Annual review Removal of disease progression following Yervoy (ipilimumab) and, if BRAF V600 mutation positive, a BRAF inhibitor and no concurrent therapy with other agents for the treatment of unresectable or metastatic melanoma
March 2016	Annual editorial review Policy number change from 5.04.50 to 5.21.50
June 2016	Annual editorial review Addition of Prescriber agrees to discontinue treatment for any immune mediated adverse reaction (encephalitis, nephritis, rash, decreased renal function and endocrinopathies) or disease progression in renewal section per SME
August 2016	Addition of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy
September 2016	Annual review
November 2016	Addition of (NSCLC) PD-L1 tumor expression with Tumor Proportion Score (TPS) ≥ 50% determined by a FDA-approved test with no prior treatment needed
December 2016	Annual review

March 2017	Addition of refractory classical Hodgkin lymphoma (cHL), who have relapsed after 3 or more prior lines of therapy Removal of the age requirement
June 2017	Annual editorial review and reference update Addition of metastatic nonsquamous non-small cell lung cancer (NSCLC) Addition of advanced or metastatic urothelial carcinoma Addition of Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers with additional requirements to criteria
July 2017	Addition of the requirement to MSI-H: diagnosis has to be confirmed by PCR-based genetic testing
September 2017	Annual review
October 2017	Addition of recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma
December 2017	Annual review
June 2018	Annual editorial review and reference update
July 2018	Addition of the diagnosis of recurrent or metastatic cervical cancer Addition of use of medication in patients with locally advanced or metastatic urothelial carcinoma in patients who are not eligible for any platinum-containing chemotherapy
August 2018	Addition of diagnosis of refractory primary mediastinal large B-cell lymphoma (PMBCL) Addition of no EGFR or ALK genomic tumor aberrations requirement to metastatic nonsquamous NSCLC
September 2018	Annual editorial review and reference update
November 2018	Annual review and reference update. Addition of indication of metastatic squamous NSCLC. Change NSCLC indication with pemetrexed and platinum chemotherapy. Addition to warnings. Addition of hepatocellular carcinoma indication
January 2019	Addition of indication: recurrent locally advanced or metastatic Merkel cell carcinoma (MCC)
March 2019	Annual review and reference update. Addition of indication of melanoma with involvement of lymph node(s) following complete resection as adjuvant treatment
April 2019	Addition of indication: Stage III NSCLC Addition of indication: Advanced renal cell carcinoma (RCC)
May 2019	Revised Metastatic NSCLC indication to include first-line therapy with TPS ≥1% and negative for EGFR or ALK tumor expression. Added hepatotoxicity monitoring requirement to RCC diagnosis

June 2019	Annual review. Added HNSCC indication used in combination with platinum and fluorouracil as first-line treatment and HNSCC as a single agent for first-line treatment with CPS >1. Added small cell lung cancer indication
August 2019	Addition of indication: Recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus. Revised Metastatic NSCLC indication
September 2019	Annual review. Addition of indication: endometrial carcinoma
January 2020	Addition of indication: Non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS). Changed initial approval duration to 12 months
March 2020	Annual review and reference update
July 2020	Addition of indications: Tumor mutational burden-high (TMB-H) solid tumors; adult indications: additional dosing regimen of 400 mg every 6 weeks; and recurrent or metastatic cutaneous squamous cell carcinoma (cSCC). Addition of indication: first-line treatment for unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC). Revised testing for MSI-H and dMMR cancers to “Diagnosis has been confirmed by polymerase chain reaction (PCR) or immunohistochemistry (IHC) test”. Revised continuation requirement that “NOT for use in MSI CNS cancers in pediatric patients” only applies to patients with solid tumors
September 2020	Annual review
October 2020	Revised cHL indication to relapsed or refractory cHL and pediatric patients with relapsed cHL must have relapsed after 2 or more lines of therapy
November 2020	Addition of indication: triple-negative breast cancer (TNBC)
December 2020	Annual review
April 2021	Revised indication per package insert: locally advanced or metastatic esophageal or gastroesophageal junction carcinoma
May 2021	Removed small cell lung cancer (SCLC) indication per latest package insert update. Addition of indication: locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma
June 2021	Annual review
July 2021	Removed requirements from MSI-H or dMMR colorectal cancer stating that Keytruda needs to be used as first-line treatment or after disease progression on fluoropyrimidine, oxaliplatin, and irinotecan. Addition of indication: locally advanced cutaneous squamous cell carcinoma. Revised Triple-Negative Breast Cancer (TNBC) indication to include patients with high-risk early stage TNBC

September 2021	Annual review. Added option to use in combination with Lenvima in advanced RCC. Removed requirement for PD-L1 CPS score for locally advanced or metastatic urothelial carcinoma.
November 2021	Added indication of persistent, recurrent, or metastatic cervical cancer used in combination with chemotherapy. Added “used as a single agent” to recurrent or metastatic cervical cancer with disease progression on or after chemotherapy
December 2021	Annual review. Added indication of adjuvant treatment of RCC in patients at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions
January 2022	Revised indication for adjuvant treatment of melanoma: no longer needs lymph node involvement and now requires Stage IIB, IIC, or III melanoma
March 2022	Annual editorial review and reference update. Per package insert update: Removed third line gastric cancer indication, i.e., “Keytruda, as a single agent, for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy”
April 2022	Addition of indication per PI update: advanced endometrial carcinoma that is MSI-H or dMMR
June 2022	Annual review and reference update
September 2022	Annual editorial review and reference update. Per PI update, added “MSI-H or dMMR tumor status, as determined by an FDA-approved test” to solid tumors and colorectal cancer diagnoses and removed PCR or IHC testing. Also added “tumor status” to endometrial carcinoma indication
February 2023	Per PI update, updated FDA-approved indications section for the additional dosing regimen and added indication of Stage IB, II, or IIIA NSCLC
March 2023	Annual review and reference update
April 2023	Per PI update, added indication of locally advanced or metastatic urothelial carcinoma in combination with Padcev (enfortumab vedotin) in patients who are not eligible for cisplatin-containing chemotherapy. Also clarified that patients with urothelial carcinoma who are not eligible for any platinum-containing chemotherapy or who have had disease progression must use Keytruda as a single agent. Per PI, deleted limitations of use for MSI-H/dMMR, edited endometrial carcinoma in combination with Lenvatinib to add pMMR into criteria
June 2023	Annual review and reference update

September 2023	Annual review and reference update
November 2023	Per PI update, added indication of resectable NSCLC in combination with platinum-containing therapy as neoadjuvant treatment, then as a single agent after surgery
December 2023	Annual review and reference update. Per PI update, added indication of biliary tract cancer and added requirement of PD-L1 CPS score for gastric cancer. Per PI update, added indication of HER2-negative gastric or gastroesophageal junction adenocarcinoma
January 2024	Per PI update, removed requirement to be ineligible for cisplatin-containing chemotherapy for urothelial carcinoma in combination with Padcev
February 2024	Per PI update, added FIGO 2014 Stage III-IVA cervical cancer
March 2024	Per PI update, removed requirement of previous treatment with sorafenib for HCC. Added requirement of HCC secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen
March 2024	Annual review and reference update
July 2024	Per PI update, added primary advanced or recurrent endometrial carcinoma
September 2024	Annual review and reference update
October 2024	Per PI update, added indication of malignant pleural mesothelioma (MPM)
December 2024	Annual review and reference update
January 2025	Revised endometrial cancer requirements to align with package insert
March 2025	Annual review and reference update
June 2025	Annual review and reference update
July 2025	Per PI update, added requirement of PD-L1 tumor expression with combined positive score (CPS) ≥1 to locally advanced or metastatic esophageal or gastroesophageal junction carcinoma and locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction. Added contraception warning to initiation and continuation. Added monitoring criterion to initiation
September 2025	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 19, 2025 and is effective on October 1, 2025.